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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte STEVEN T. BOYCE

Appeal 2008-4764[1]
Application 10/092,237
Technology Center 1600

Decided:[2] February 25, 2009

Before DONALD E. ADAMS, LORA M. GREEN, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1-4, 6, 7, 9-13, 15-18, 21-30, and 32-37, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Heard February 3, 2009.

[2] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 CFR § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

STATEMENT OF THE CASE

The claims are directed to a cultured skin device (claims 1-4, 6, 7, 9, and 28); a method of producing a cultured skin device (claims 10-13, 15-18, 21-23, 29, and 30); a method for producing a permanent cultured skin device (claims 24-27 and 34-37); and a method of inoculating a matrix with a cell suspension (claims 32 and 33).

Claims 1, 10, 24, 32, and 34 are illustrative:

1. A cultured skin device comprising cultured dermal cells on an engineered biocompatible reticulated acellular matrix comprised of collagen, the dermal cells providing a cellular lamination layer for cultured epidermal cells deposited thereon.

10. A method of producing a cultured skin device comprising inoculating an engineered biocompatible reticulated acellular matrix comprised of collagen with cultured dermal and epidermal cells, and incubating said inoculated matrix under conditions sufficient to form a cultured skin device, the dermal cells providing a cellular lamination layer for the epidermal cells.

24. A method for producing a permanent cultured skin device for a burn patient comprising

isolating at least one dermal cell type and at least one epidermal cell type from an uninjured area of skin from a burn patient,

separately culturing the isolated dermal and epidermal cells,

inoculating an engineered biocompatible reticulated acellular matrix comprised of collagen with the cultured dermal and epidermal cells and incubating the inoculated matrix under conditions for form a cultured skin device having a dermal cellular lamination layer to support an epidermal cellular layer deposited thereon within one month after inoculating the cells, and

providing the device to the patient.

32. A method of inoculating a matrix with a cell suspension comprising

providing an engineered reticulated acellular matrix comprised of collagen overlying an absorbent material, the material saturated with a cell culture medium,

thereafter providing dermal cells suspended in a volume of culture medium to a topic surface of the matrix under conditions sufficient to draw the medium through the absorbent material and deposit the dermal cells on the matrix to form a cellular lamination layer.

34. A method for producing a permanent cultured skin device for a patient comprising

isolating at least one dermal cell type and at least one epidermal cell type from an uninjured area of skin from the patient,

separately culturing the isolated dermal and epidermal cells,

inoculating an engineered biocompatible reticulated acellular matrix comprised of collagen with the cultured dermal and epidermal cells and incubating the inoculated matrix under conditions to form a cultured skin device having a cellular lamination layer on the biocompatible reticulated acellular matrix within one month after inoculating the cells, and

providing the device to the patient.

The Examiner relies on the following prior art references to show unpatentability:

Boyce (Boyce I) US 5,976,878 Nov. 2, 1999

Krejci et al., *In Vitro Reconstitution of Skin: Fibroblasts Facilitate Keratinocyte Growth and Differentiation on Acellular Reticular Dermis*, 97(5) J. Invest. Dermatol. 843-848 (1991).[3]

Boyce (Boyce II), *Skin substitutes from cultured cells and collagen-GAG polymers,* 37 Med. Biol. Eng. Comput. 791-800 (1998).

Naughton, *From Lab Bench to Market Critical Issues in Tissue Engineering,* 961 Ann. N.Y. Acad. Sci. 372-385 (2002).

[3] The Examiner and Appellant refer to this reference as "Niels" (*see, e.g.,* Ans. 3 and App. Br. 7).

Supp et al., *Human dermal microvascular endothelial cells form vascular analogs in cultured skin substitutes after grafting to athymic mice,* 16 The FASEB Journal 797-804 (2002).

Appellant relies on the following evidence:

Declaration of Steven T. Boyce (First Boyce Dec.), executed March 25, 2004.

Declaration of Steven T. Boyce (Second Boyce Dec.), executed August 1, 2005.

Boyce (Boyce Slides), Power Point Slides, exhibited during an Examiner's Interview on July 20, 2005.

The rejections as presented by the Examiner are as follows:

1. Claims 10-13, 15-18, 21-27, and 34-37 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite.[4]

2. Claims 1-4, 6, 7, 9-13, 15-18, 21-30, and 32-37 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

3. Claims 1-4, 6, 7, 9-11, 13, 15, 18, 21-27, 29, and 32-37 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Krejci.

4. Claims 12, 16, 17, 28, and 30 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Krejci, Boyce I, and Boyce II.

We reverse the rejection of claims 10-13, 15-18, 21-27, and 34-37 under 35 U.S.C. § 112, second paragraph.

We reverse the rejection of claims 1-4, 6, 7, 9-13, 15-18, 21-30, and 32-37 under the enablement provision of 35 U.S.C. § 112, first paragraph.

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[4] While the Examiner includes claims 14, 19, and 20 in the statement of this rejection, these claim have been cancelled and are therefore not before this panel (*see, e.g.,* App. Br. 2; Reply Br. 10).

We affirm the rejection of claims 1-4, 6, 7, 9-11, 13, 15, 18, 21-27, 29, and 32-37 under 35 U.S.C. § 102(b) as being anticipated by Krejci.

We affirm the rejection of claims 12, 16, 17, 28, and 30 under 35 U.S.C. § 103(a) as unpatentable over the combination of Krejci, Boyce I, and Boyce II.

DEFINITENESS:

PRINCIPLES OF LAW

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

Claims are in compliance with 35 U.S.C. § 112, second paragraph, if "the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1987).

Claims 10-13 and 15-17:

ISSUE

Did the Examiner meet his burden of establishing that claim 10 is indefinite?

FINDINGS OF FACT

FF 1. The Examiner finds that claim 10 is indefinite in the recitation of the phrase "conditions sufficient to form a cultured skin device so that the

dermal cells provide a cellular lamination layer" (Ans. 9 (emphasis removed)).

FF 2. The Examiner finds that "the scope of conditions sufficient to form a cultured skin device is not limited to [s]equential or simultaneous inoculation of cells" (Ans. 10).

FF 3. Appellant's Specification teaches that dermal and epidermal cells can be inoculated onto a matrix either sequentially or simultaneously as "combinations of dermal and epidermal cells" (Spec. 16: 18- 17: 6).

ANALYSIS

The Examiner finds that from the conditions recited in claim 10 (FF 1) "[i]t is unclear whether the dermal and epidermal cells are inoculated as a mixture or separately" (Ans. 9).

Appellant contends that since "no temporal limitation is recited in claim 10" the cells can be inoculated onto the matrix "either sequentially or simultaneously" (App. Br. 21 (emphasis removed); *see also* FF 3).

The Examiner maintains the rejection because "the scope of conditions sufficient to form a cultured skin device is not limited to [s]equential or simultaneous inoculation of cells" (FF 2). We are not persuaded.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d at 875; *see also Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1385 (claims are in compliance with 35 U.S.C. § 112, second paragraph, if "the claims, read

in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits.")

Appellant's Specification discloses that the dermal and epidermal cells can be inoculated onto a matrix either sequentially or simultaneously (FF 3). Claim 10 is open to either sequential or simultaneous inoculation of a matrix. The Examiner has failed to explain why a person of ordinary skill in this art would read claim 10 to include any other "condition" beyond sequential or simultaneous inoculation.

CONCLUSION OF LAW

The Examiner failed to meet his burden of establishing that claim 10 is indefinite. Claims 11-13 and 15-17 depend from claim 10.

The rejection of claims 10-13 and 15-17 under 35 U.S.C. § 112, second paragraph, as indefinite is reversed.

Claims 18, 21-27 and 34-37:

ISSUE

Did the Examiner meet his burden of establishing that claim 18 is indefinite?

FINDINGS OF FACT

FF 4. The Examiner finds that claim 18 is indefinite in the recitation of the phrase "conditions to form at least one dermal cellular lamination layer" (Ans. 10 (emphasis removed)).

FF 5. The Examiner finds that claim 24 is indefinite in the recitation of the phrase "conditions to form a permanent cultured skin device having a dermal cellular lamination layer" (Ans. 10 (emphasis removed)).

FF 6. The Examiner finds that claim 34 is indefinite in the recitation of the phrase "conditions to form a permanent cultured skin device within one month having a cellular lamination layer" (Ans. 10 (emphasis removed)).

FF 7. The Examiner finds that the "scope of conditions sufficient to form a cultured skin device is not limited to the identification of [a] first dermal cell" (Ans. 10).

FF 8. The Examiner finds that "standard tissue culture conditions would not lead to the formation of at least one dermal cellular lamination layer because standard tissue culture condition[s] produce[ ] a monolayer and not a cellular lamination layer which constitutes multiple layers of dermal cells" (Ans. 24 and 25 (emphasis removed)).

FF 9. Appellant's Specification discloses that "dermal and epidermal cells are individually cultured as described by Boyce and Ham in *J. Invest. Dermatol.* 1983;81:335, and chapter 28 in *Methods in Molecular Medicine, Vol.* 18, p.365, Morgan & Yarmush, Eds., Humana Press, Totowa NJ (1998), both of which are expressly incorporated by reference herein" (Spec. 10: 6-10).

FF 10. Appellant's Specification discloses that "[a]fter inoculation, the device is incubated under conditions facilitating cell growth, maintenance, and division . . . . The cells form a substantially continuous monolayer or multilayer surface" (Spec. 20: 21-24).

ANALYSIS

The Examiner maintains the rejection of claim 18 because the "scope of the conditions sufficient to form a cultured skin device is not limited to the identification of first dermal cell" (Ans. 10). Claim 18 does not,

however, require "the identification of [a] first dermal cell". Instead, claim 18 requires the isolation of "at least a first dermal cell type from skin" (Claim 18). We do not find this phrase indefinite.

Nevertheless, we recognize that claim 18 requires the inoculation of a "matrix under conditions to form at least one dermal cellular lamination layer population" (*id.*). The Examiner finds that "a cellular lamination layer . . . constitutes multiple layers of dermal cells" (FF 8). Therefore, the Examiner concludes that "standard tissue culture conditions would not lead to the formation [of] at least one dermal cellular lamination layer because standard tissue culture condition[s] produce[ ] a monolayer" (*id.*). The Examiner makes a similar argument for claims 24 and 34 (*id.*).

However, as Appellant explains

> a cellular lamination includes <u>one or more</u> layers of the same cell type. The cellular lamination layer (lamina) is on the surface of the matrix. The cellular lamination layer may or may not be a monolayer. The matrix itself is a separate layer (lamina). The cellular lamination layer on the matrix constitutes a multi-laminate structure.

(Reply Br. 12.) In addition, Appellant's Specification discloses that "[t]he cells form a substantially continuous monolayer or multilayer surface" (FF 10). Accordingly, we are not persuaded by the Examiner's unsupported assertions to the contrary.

Further, for the reasons set forth with regard to claim 10, we are not persuaded by the Examiner's finding that claims 24 and 34 are not limited to sequential or simultaneous inoculation of cells (FF 7).

CONCLUSION OF LAW

The Examiner failed to meet his burden of establishing that claim 18 is indefinite. The rejection of claims 18, 21-27 and 34-37 under 35 U.S.C. § 112, second paragraph, as indefinite is reversed.

ENABLEMENT:

ISSUE

Did the Examiner meet his burden of establishing that Appellant's Specification fails to provide an enabling description of the claimed invention?

FINDINGS OF FACT

FF 11. Appellant's Specification discloses that "[i]n preparing the device, any biocompatible material that is permissive as a substrate for culture and transplantation of cultured cells may be used" (Spec. 11: 4-6).

FF 12. Appellant's Specification discloses the preparation of a crosslinked matrix (Spec. 13: 1 - 15: 17).

FF 13. The Examiner finds that while Appellant's Specification provides an enabling description of a "biocompatible reticular acellular matrix [that] is a porous cross-linked collagen matrix"; Appellant's Specification "does not reasonably provide enablement for any cultured skin device, wherein the biocompatible reticular acellular matrix is composed of any other substance" (Ans. 6).

FF 14. The Examiner finds that "[t]he scope of invention as claimed encompasses an artificial skin device made of any biocompatible reticulated a cellular [sic] matrix (i.e. steel, glass, gold, plastic etc)" (Ans. 7).

FF 15. The Examiner finds that "[t]he state of the artificial skin art at the time of filing of [the] instant invention was such that the construction [of] artificial skin is complex and the final product made is of little benefit if it cannot be efficiently produced, and is capable of providing engraftment benefits (see Supp . . . page 803, col.1)" (*id.*).

FF 16. The Examiner finds that

> The state of the art regarding the selection of the matrix onto which the cells are seeded suggest that the choice of the matrix has been found to be key to the uniform formation of tissue, since the matrix provides physical and chemical cues to guide the process of artificial skin development. In addition the spatial and compositional properties of the matrix are key, with porosity of the scaffold and inter connectivity of the pores being capable of enabling cell penetration into the structure as well as transport of nutrients and waste products (Naughton).

(Ans. 7-8.)

FF 17. The Examiner finds that Appellant "fails to provide any evidence on the record, which establishes that a skin device constructed on a non-porous acellular matrix is capable of engrafting for the therapy of [*inter alia*] a burn" (Ans. 8).

FF 18. Naughton teaches that

> [t]he optimization of scaffolds onto which cells are seeded has . . . been found to be key to the uniform formation of tissue, with scaffolds that provide physical and chemical cues to guide the process. Scaffolds are porous structures fabricated from natural materials such as collagen and fibrin or from synthetic materials such as degradable polyesters used in surgical sutures. Scaffolds take forms ranging from sponge-like sheets and fabrics to gels to highly complex structures with intricate pores and channels made with new materials processing technologies. The spatial and compositional properties of the scaffold are key, with the porosity of the scaffold and interconnectivity of the

> pores being capable of enabling cell penetration into the structure as well as the transport of nutrients and waste products.

(Naughton 374: 16-25.)

FF 19. Boyce declares that "the claimed cultured skin device contains 'cultured dermal cells on a biocompatible reticulated matrix'" (First Boyce Dec. 2: ¶6). "The claims also recited that the dermal cells provide a cellular lamination layer. In my opinion, this additionally indicates that the dermal cells do not fill the matrix" (First Boyce Dec. 3: ¶ 7).

FF 20. Boyce declares that a matrix that is reticulated is continuous and has no perforations, "that is, it has [no] pores or holes forming direct channels from a top to bottom surface" (Second Boyce Dec. 1: ¶ 4).

FF 21. Appellant's Specification discloses that

> Because the matrix is reticulated and thus contains multiple continuous surfaces, as opposed to being perforated with direct channels or openings from a top surface to a bottom surface, the fibroblasts or other dermal cells being inoculated need not fill these channels or openings in the matrix before the epidermal cells may be added. Rather, upon inoculation, the dermal cells attach to the reticulations, and thus are able to provide a continuous surface lamination for the subsequently inoculation of epidermal cells within a shorter time period than is possible using a perforated matrix.

(Spec. 20: 12-20.)

FF 22. Boyce Declares that his "device does not require perforations because it is sufficiently biocompatible itself to conduct fluids (e.g., nutrients in, and wastes out)" (Second Boyce Dec. 2: ¶ 5).

PRINCIPLES OF LAW

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Id.* at 1561, (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk A/S,* 108 F.3d 1361, 1365 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1374 (Fed. Cir. 1999). Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

ANALYSIS

Appellant's Specification discloses that the claimed device can be made from any biocompatible material that is both permissive (1) as a substrate for culture; and (2) to the transplantation of cultured cells (FF 11). In addition, every claim before us on appeal requires that the reticulated

acellular matrix comprises collagen (*see, e.g.,* App. Br. 15). The Examiner provides no evidence to suggest that a biocompatible material that meets these requirements would not be capable of being used in the device of Appellant's claimed invention.

Accordingly, we find that the preponderance of the evidence on this record regarding the components of the biocompatible material falls in favor of Appellant.

Appellant's matrix is reticulated, according to Boyce this means the matrix "is continuous and has no perforations" (FF 20). We recognize the Examiner's concern that Appellant "fails to provide any evidence on the record, which establishes that a skin device constructed on a non-porous acellular matrix is capable of engrafting for the therapy of [*inter alia*] a burn" (FF 17). We also recognize that the scaffolds discussed in Naughton Scaffolds are porous structures and that the optimization of scaffolds onto which cells are seeded has been found to be key to the uniform formation of tissue (FF 18). In this regard, we recognize that Naughton teaches that "[t]he spatial and compositional properties of the scaffold are key, with the porosity of the scaffold and interconnectivity of the pores being capable of enabling cell penetration into the structure as well as the transport of nutrients and waste products" (*id.*).

Nevertheless, we recognize that Appellant's Specification distinguishes between perforated matrices and reticulated matrices, disclosing that "dermal cells attach to the reticulations, and thus are able to provide a continuous surface lamination for the subsequently inoculation of epidermal cells within a shorter time period than is possible using a perforated matrix" (FF 21; *see also* Reply Br. 8). Further, we recognize in

Boyce's declaration that his "device does not require perforations because it is sufficiently biocompatible itself to conduct fluids (e.g., nutrients in, and wastes out)" (FF 22). We also recognize Appellant's contention that "Appellant himself (with his representative) sat with the Examiner at the July 20, 2005 personal interview (two years ago) and showed four color slides demonstrating recovery of a burn patient treated with the claimed device at four different postoperative days" (Reply Br. 9; *see also* Boyce Slides).

Taken together we find that the preponderance of the evidence on this record regarding the use of non-perforated matrices falls in favor of Appellant.

CONCLUSION OF LAW

The Examiner failed to meet his burden of establishing that Appellant's Specification fails to provide an enabling description of the claimed invention.

The rejection of claims 1-4, 6, 7, 9-13, 15-18, 21-30, and 32-37 under the enablement provision of 35 U.S.C. § 112, first paragraph is reversed.

ANTICIPATION:

Appellant provides separate arguments for the following groups of claims: I. claims 1-4, 6, 7, and 9; II. claims 10-13, 15-18, 21-27, 29, and 30; III. claims 32 and 33; and IV. claims 34-37. Claims 1, 10, 32, and 34 are representative. We take each in turn below.

PRINCIPLES OF LAW

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

In re Oetiker, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

It is well settled that, "[t]o anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

It is also well settled that during examination, the PTO must interpret terms in a claim using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

> [D]uring patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed. . . . An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.

In re Zletz, 893 F.2d 319, 321-22 (Fed. Cir. 1989).

Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii) ("Any arguments or authorities not included in the brief or a reply brief ... will be refused consideration by the Board, unless good cause is shown.").

Claim 1:

ISSUE

Is the Examiner's prima facie case of anticipation supported by a preponderance of the evidence on this record?

FINDINGS OF FACT

FF 23. The Examiner finds that Krejci "teaches a cultured skin device comprising cultured dermal cells (fibroblasts) on a biocompatible acellular reticular dermal matrix, wherein the dermal cells provides a lamination layer for cultured epidermal cells (keratinocytes) deposited on the dermal cells (page 844, col.1 para. 2, page 845, col.2 para. 2)" (Ans. 4).

FF 24. Krejci teaches the preparation of an acellular reticular dermal matrix from skin harvested from a cadaver (Krejci 843: col. 2, ll. 15-37). The Examiner finds that Krejci "teaches that the acellular reticular dermal matrix comprises collagen (page 845, fig-1a)" (*id.*).

FF 25. The Examiner finds that Krejci "teaches preparation of cultured skin device using air-liquid interface culture system (page 844, col.1 para.1)" (*id.*).

FF 26. The Examiner finds that Krejci "teaches grafting of the cultured skin device on an athymic mouse, which resulted in reconstruction of skin populated with blood vessels at day 25, wherein the overlying epidermis was viable and differentiated (page 844, col.1 para.3, page 845[ ]col.2 para. 2)" (*id.*).

FF 27. The Examiner finds that Appellant's claims encompass "any biocompatible reticulated acellular matrix that has been engineered by man" (Ans. 12). The Examiner finds that Krejci's biocompatible matrix is

"engineered" because Krejci teaches the "irradiattion [sic] of the harvested skin (to devitalize it), soaking it in antibiotics (to sterilize it), and removing a portion of it to obtain de-epidermized dermis" (*id.*). The Examiner finds that "the biocompatible marix [sic] as claimed is not limited to an engineered matrix prepared or fabricated from chemicals" (*id.*).

FF 28. Appellant's Specification discloses that the device may comprise a collagen matrix, wherein the collagen may be from "human sources" and that "[o]ther proteins such as elastin or reticulin, or polymers of amino acids, whether naturally occurring or synthetic, may be used" (Spec. 11: 4-15).

FF 29. Krejci teaches that "[s]eeding cultured dermal fibroblasts on SCD [(reticular second-cut dermis)] resulted in both colonization of the surface as well as invasion of the acellular dermis" (Krejci 845: col. 2, ll. 18-20). Krejci teaches that "[s]kin explants placed on fibroblast conditioned SCD grew out an average of 7.6 mm^2 in 2 weeks" (Krejci 845: col. 2, ll. 20-21).

FF 30. Boyce declares that "the claimed cultured skin device contains 'cultured dermal cells on a biocompatible reticulated matrix'" (First Boyce Dec. 2: ¶6). "The claims also recited that the dermal cells provide a cellular lamination layer. In my opinion, this additionally indicates that the dermal cells do not fill the matrix" (First Boyce Dec. 3: ¶ 7).

ANALYSIS

Claim 1 is drawn to a cultured skin device. The device of claim 1 comprises (1) cultured dermal cells on (2) an engineered biocompatible reticulated acellular matrix comprised of collagen. Claim 1 requires the dermal cells to provide a cellular lamination layer for cultured epidermal cells deposited thereon.

Krejci "teaches a cultured skin device comprising cultured dermal cells (fibroblasts) on a biocompatible acellular reticular dermal matrix, wherein the dermal cells provides a lamination layer for cultured epidermal cells (keratinocytes) deposited on the dermal cells (page 844, col.1 para. 2, page 845, col.2 para. 2)" (FF 23). Krejci's "acellular reticular dermal matrix comprises collagen" (FF 24). According to Appellants, a matrix that is reticulated is continuous and has no perforations (FF 20).

The device of claim 1 comprises cultured dermal cells on an engineered biocompatible reticulated acellular matrix comprised of collagen (Claim 1; FF 30). Krejci teaches seeding cultured dermal fibroblasts on a reticulated acellular matrix (FF 29). Krejci's reticulated acellular matrix is engineered and biocompatible (FF 23, 24, and 27).

Appellant contends that he "has given his claim term 'engineered' a specific meaning that limits the claim scope to a particular structure" (App. Br. 8). More specifically, Appellant contends that the use of the term "engineered matrix" refers to a "chemically fabricated matrix" (App. Br. 9) or "one that is synthesized from chemicals and fabricated to desired specifications" (Reply Br. 4). We are not persuaded.

Appellant has not identified, and we do not find, a definition of the term "engineered" in Appellant's Specification. While Appellant has identified portions of his Specification, which describes the preparation of a matrix; Appellant has not identified, and we do not find, a definition of the term matrix in Appellant's Specification that limits the scope of the term to a "chemically fabricated matrix". In this regard, we recognize Appellant's reliance on page 11, lines 16-17 of their Specification, which describes "one embodiment of preparing the matrix" (App. Br. 8). We are not persuaded

that this "one embodiment of preparing the matrix" or Appellant's disclosure of a "Matrix-Forming Protein-Containing Fluid" and the "Preparation of Crosslinked Matrix (App. Br. 8-9) limits the scope of the term matrix, as it appears in Appellant's claims to a "chemically fabricated matrix".

According to Appellant's Specification the device may comprise a collagen matrix, wherein the collagen may be from "human sources" (FF 28). Krejci teaches a collagen matrix obtained from human sources (FF 27). Further, as the Examiner explains, Krejci's matrix is obtained through the use of a number of manipulative steps, e.g., it was engineered by the removal of cells, sterilization, etc. (*id.*).

For the foregoing reasons, we find no error in the Examiner's finding that Krejci's matrix is an engineered biocompatible reticulated acellular matrix comprised of collagen.

Appellant contends that "Appellant acquiesces to the Examiner's proposed amendment clarifying that his matrix is 'chemically engineered', because that has been Appellant's position throughout" (Reply Br. 4). This is not, however, what has been presented to this panel for review. Appellant could have amended the claims to clarify his intention that the matrix be "chemically engineered" during prosecution. *In re Zletz*, 893 F.2d at 321-22. He did not.

Appellant contends that their "dermal cells are not *required* to fill the matrix" (App. Br. 10 (emphasis added)). There is, however, no requirement in Appellant's claims that dermal cells seeded onto the matrix do not also invade the matrix (*see e.g.,* FF 21). Further, we are not persuaded by Appellant's contention that Krejci *requires* the dermal cells to invade the substrate (App. Br. 10). Krejci teaches that by seeding cultured dermal

fibroblasts on a reticulated collagen matrix the cells colonized the surface and invaded the acellular dermis (FF 29). Despite Appellant's contention to the contrary, we do not find a teaching in Krejci that *requires* the dermal cells to invade the matrix.

In addition, Krejci teaches that "[s]kin explants placed on fibroblast conditioned SCD grew out an average of 7.6 mm^2 in 2 weeks" (FF 29). Thus, we find that a person of ordinary skill in the art would recognize that Krejci's dermal cells provide a cellular lamination layer for cultured epidermal cells deposited thereon.

In sum, there is no persuasive evidence on this record to support a conclusion that Krejci's matrix is different from Appellant's. For the foregoing reasons, we find no error in the Examiner's prima facie case of anticipation. Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii).

CONCLUSION OF LAW

The Examiner's prima facie case of anticipation is supported by a preponderance of the evidence on this record.

The rejection of claim 1 under 35 U.S.C. § 102(b) as being anticipated by Krejci is affirmed. Because they are not separately argued, claims 2-4, 6, 7, and 9 fall together with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 10:

ISSUE

Did Appellant meet his burden of establishing that the Examiner's prima facie case of anticipation is in err?

ANALYSIS

Claim 10 is reproduced above.

Appellant contends that Krejci "does not disclose an engineered matrix, nor does . . . [Krejci] have a cellular lamination layer, as the terms are properly construed" (App. Br. 11). For the reasons set forth above, we are not persuaded by Appellant's contentions.

CONCLUSION OF LAW

Appellant failed to meet his burden of establishing that the Examiner's prima facie case of anticipation is in err.

The rejection of claim 10 under 35 U.S.C. § 102(b) as being anticipated by Krejci is affirmed. Because they are not separately argued, claims 11, 13, 15, 18, 21-27, and 29 fall together with claim 10. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 32:

ISSUE

Did Appellant meet his burden of establishing that the Examiner's prima facie case of anticipation is in err?

ANALYSIS

Claim 32 is reproduced above.

Appellant contends that Krejci does not disclose an engineered matrix "as the terms are properly construed" (App. Br. 11). In addition, Appellant contends that the "dermal cells on the surface of the matrix . . . are not

required to invade the matrix" (*id.*). For the reasons set forth above, we are not persuaded by Appellant's contentions.

CONCLUSION OF LAW

Appellant failed to meet his burden of establishing that the Examiner's prima facie case of anticipation is in err.

The rejection of claim 32 under 35 U.S.C. § 102(b) as being anticipated by Krejci is affirmed. Because it is not separately argued, claim 33 falls together with claim 32. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 34:

ISSUE

Did Appellant meet his burden of establishing that the Examiner's prima facie case of anticipation is in err?

ANALYSIS

Claim 34 is reproduced above.

Appellant contends that "[f]ibroblasts, which are dermal cells, that invade . . . [Krejci's] acellular dermis do not meet Appellant's claimed limitation that requires a cellular lamination layer in which cells do not invade the matrix" (App. Br. 11). In addition, Appellant contends that Krejci "does not disclose such a matrix, as the terms are properly construed" (App. Br. 12).

Notwithstanding Appellant's contention to the contrary, claim 34 does not require "a cellular lamination layer in which cells do not invade the

matrix". Accordingly, for the reasons set forth above, we are not persuaded by Appellant's contentions.

CONCLUSION OF LAW

Appellant failed to meet his burden of establishing that the Examiner's prima facie case of anticipation is in err.

The rejection of claim 34 under 35 U.S.C. § 102(b) as being anticipated by Krejci is affirmed. Because they are not separately argued, claims 35-37 fall together with claim 34. 37 C.F.R. § 41.37(c)(1)(vii).

OBVIOUSNESS:

Appellant provides separate arguments for the following groups of claims: I. claim 12; II. claims 16 and 17; III. claim 28; and IV. claim 30. Claim 16 is representative of Group II. We take each Group in turn below.

PRINCIPLES OF LAW

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). On appeal to this Board, Appellants must show that the Examiner has not sustained the required burden. *See* (1) *Ex parte Yamaguchi*, http://www.uspto.gov/web/offices/dcom/bpai/ prec/fd074412.pdf, slip op. at 5 and 23 (BPAI Aug. 29, 2008) (precedential); (2) *Ex parte Fu*, http://www.uspto.gov/web/offices/ dcom/bpai/prec/fd080601.pdf, slip op. at 5 and 20 (BPAI Mar. 31, 2008) (precedential); (3) *Ex parte Catan*, http://www.uspto.gov/web/ offices/dcom/bpai/prec/fd070820.pdf, slip op. at

3 and 21 (BPAI Jul. 3, 2007) (precedential), and (4) *Ex parte Smith*, http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf, slip op. at 4, 9 and 23 (BPAI Jun. 25, 2007).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 1739 (2007).

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103.

Id. at 1742. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 127 S.Ct. at 1741. *See also id.* at 1742 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

Where "a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation." *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997). Statements of intended use often appear in the claim's preamble, although not necessarily. *In re Stencel*, 828 F.2d 751, 754 (Fed. Cir. 1987). "An intended use or purpose usually will not limit the

scope of the claim because such statements usually do no more than define a context in which the invention operates." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003).

> "Where a product-by-process claim is rejected over a prior art product that appears to be identical, although produced by a different process, the burden is upon the applicants to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Best*, 562 F.2d [1252,] 1255 . . . [(CCPA 1977)]."

In re Marosi, 710 F.2d 799, 803 (Fed. Cir. 1983).

It is well settled that argument by counsel cannot take the place of evidence. *In re Cole*, 326 F.2d 769, 773 (CCPA 1964); *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

Claim 12:

ISSUE

Did Appellant meet his burden of establishing that the Examiner's prima facie case of obviousness is in err?

FINDINGS OF FACT

FF 31. The Examiner relies on Krejci as discussed above (Ans. 5).

FF 32. The Examiner finds that Krejci "does not specifically teach a method of producing a cultured skin device in medium containing insulin in the range of 0.05 µg/ml to about 500 mg/ml" (*id.*).

FF 33. Krejci teaches the culture of fibroblasts in DMEM with 10% bovine calf serum and antibiotics (Krejci 844: col. 1, ll. 5-7). Krejci teaches the

culture of keratinocytes in a 3:1 mixture of DMEM and Ham's F12 supplemented with, *inter alia*, 5 u/ml insulin (Krejci 844: col. 1, ll. 32-34). FF 34. Boyce I teaches "HK cultures were initiated from human surgical discard specimens and cultured in nutrient medium MCDB 153 containing [*inter alia*] 5 µg/ml insulin" (Boyce I, col. 14, ll. 60-64; Ans. 5). Boyce I teaches that "[t]he cells are cultured under optimal conditions which includes using a growth permissive culture medium such as MCDB 153 containing elevated amounts of . . . insulin" (Boyce I, col. 7, ll. 8-11).

ANALYSIS

Claim 12 depends ultimately from and further limits the conditions of claim 10 to comprise incubating in a medium containing a component selected from the group consisting of insulin, at least one essential fatty acid, vitamin C, and combinations thereof, wherein insulin is at a concentration in the range of about 0.05 µg/ml to about 500 mg/ml.

Based on the foregoing evidence (FF 31-34) the Examiner concludes that "it would have been obvious to one [of] ordinary skill in the art at the time of filing to incorporate insulin in the range of 0.05 µg/ml to about 500 [m]g/ml in the culture conditions as taught by . . . [Krejci] in view of Boyce [I]" (Ans. 6). The Examiner finds that "[o]ne would have been motivated to incorporate insulin in culture media because insulin is a growth factor that increases cellular growth and proliferation" (*id.*).

Appellant contends that Krejci "does not use a medium for incubating an engineered matrix for the reasons set forth and analyzed above" (App. Br. 13). For the reasons set forth above, we are not persuaded.

Appellant contends that Krejci does not "add insulin in the medium" (App. Br. 13). While Krejci teaches an insulin containing media (FF 33), the Examiner finds that Krejci "does not specifically teach a method of producing a cultured skin device in medium containing insulin in the range of 0.05 μg/ml to about 500 mg/ml" (FF 32).

Appellant contends that Boyce II "discloses a completely different device, one in which the matrix is filled uniformly and entirely with cultured dermal cells" (App. Br. 13; FF 19). Appellant fails, however, to explain why the type of device would affect the choice of media, e.g., a medium containing insulin, used to culture Krejci's skin device. We are not persuaded by Appellant's contention that Boyce I fails to identify the medium in which the device is incubated (Reply Br. 7). There is no evidence on this record (including the First and Second Boyce Declarations) to support a finding that a person of ordinary skill in the art would interpret the prior art to establish that different culture media are required for different skin devices, or that a different culture media would be required to culture cells, as opposed to culturing cells on a skin device. Therefore, we are not persuaded by Appellant's contention that "it cannot be assumed that results from selective cell culture in monolayer (or any other culture condition) will translate to combination cultures in three dimensions" (Reply Br. 7). It is well settled that argument by counsel cannot take the place of evidence. *In re Cole*, 326 F.2d at 773; *In re Geisler*, 116 F.3d at 1471.

For the same reasons, we are not persuaded by Appellant's contention that his invention has satisfied an "unmet need" (Reply Br. 7).

Accordingly, we find no error in the Examiner's prima facie case of obviousness, wherein one would use the culture media taught by Boyce I to

culture cells on Krejci's device; or in the alternative incorporated that "[o]ne would have been motivated to incorporate insulin in culture media because insulin is a growth factor that increases cellular growth and proliferation" (Ans. 6).

CONCLUSION OF LAW

Appellant failed to meet his burden of establishing that the Examiner's prima facie case of obviousness is in err.

The rejection of claim 12 under 35 U.S.C. § 103(a) as unpatentable over the combination of Krejci, Boyce I, and Boyce II is affirmed.

Claim 16:

ISSUE

Did Appellant meet his burden of establishing that the Examiner's prima facie case of obviousness is in err?

FINDINGS OF FACT

FF 35. The Examiner finds that Boyce II teaches "skin substitutes comprising cultured human keratinocytes, fibroblasts, melanocytes and collagen-GAG polymers" (Ans. 5). In addition, the Examiner finds that Boyce II "teaches that components of skin substitute include [*inter alia*] . . . melanocytes . . . (page 792, col. 1, table-1, page 793 fig-1)" (*id.*). Boyce II teaches "[p]igment cells, the melanocytes, have also been cultured and transplanted for treatment of vitiligo . . . and added to cell-polymer constructs" (Boyce II, 792, col. 1, ll. 22-25).

ANALYSIS

Claim 16 depends from claim 10 and further requires the epidermal cells to comprise melanocytes. While claim 16 recites the phrase "the cultured skin composition restores skin pigmentation", we find this recitation to be a statement of intended use as there is no requirement in claim 10 to administer the device to a patient.

Appellant contends that "Appellant's above analysis with respect to claim 12 applies with respect to claims 16-17" (App. Br. 13). For the reasons set forth above, we are not persuaded.

Appellant contends that the Examiner failed to establish that the specific cells recited in claim 16 were obvious in view of the combination of art relied upon (*id.*). In this regard, Appellant contends that Boyce II "does not teach the specific combination of materials for use as a skin substitute. It teaches only hypothetical candidate materials" (Reply Br. 6). We are not persuaded.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. 398, 127 S. Ct. at 1740. Further, it is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 127 S.Ct. at 1741. *See also id.* at 1742 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). Here, while Appellant characterizes Boyce II's identification of e.g., melanocytes as a hypothetical candidate material, we find that a person of ordinary creativity would have utilized melanocytes in Krejci's device for pigmentation (FF 31 and 35).

CONCLUSION OF LAW

Appellant failed to meet his burden of establishing that the Examiner's prima facie case of obviousness is in err.

The rejection of claim 16 under 35 U.S.C. § 103(a) as unpatentable over the combination of Krejci, Boyce I, and Boyce II is affirmed. Because it is not separately argued, claim 17 falls together with claim 16. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 28:

ISSUE

Did Appellant meet his burden of establishing that the Examiner's prima facie case of obviousness is in err?

ANALYSIS

Claim 28 is drawn to a cultured skin device. The claim is written in product-by-process format and identifies the process utilized to prepare the product as comprising the following four steps:

(1) isolating at least one dermal cell type and at least one epidermal cell type from skin,

(2) separately culturing the isolated dermal and epidermal cells,

(3) providing the cultured dermal cells to an engineered biocompatible reticulated acellular matrix comprised of collagen and incubating in Dulbecco's modified Eagle's medium containing strontium chloride (0.01 mM to 100 mM); linoleic acid/BSA (0.02 μg/ml to 200 μg/ml); insulin (0.05 μg/ml to 500 μg/ml); triiodothyronine (0.2 pM to 2000 pM); hydrocortisone (0.005 μg/ml to 50 μg/ml); a combination of penicillin (100 U/ml), streptomycin (100 μg/ml), amphotericin (0.25 μg/ml); ascorbic acid-2-phosphate (0.001mM to 10 mM), progesterone (0.1 nM to 1000 nM) and epidermal growth factor (0.01 ng/ml to 100 ng/mo) for about 24 hours, and

(4) thereafter providing the cultured epidermal cells on a cellular lamination layer of dermal cells to form the cultured skin device.

Appellant contends that

> [o]ne skilled in the art would not be taught, motivated, or suggested to omit or add a component, or to change a concentration of any component, at least because there is no suggestion to do so in these references and there is no reasonable expectation of success that doing so would result in the desired outcome. In contrast, requiring specific components at specified concentrations teaches away from any change, because of the possibility that such change would perturb the balance required for growth and maintenance of specific cell types.

(App. Br. 14.) We are not persuaded.

Appellant has provided no evidence to support a conclusion that the device of claim 28 is different from the device taught by the combination of Krejci, Boyce I, and Boyce II. In this regard, we note that

> "[w]here a product-by-process claim is rejected over a prior art product that appears to be identical, although produced by a different process, the burden is upon the applicants to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Best*, 562 F.2d [1252,] 1255 . . . [(CCPA 1977)]."

In re Marosi, 710 F.2d 799, 803 (Fed. Cir. 1983). It is well settled that argument by counsel cannot take the place of evidence. *In re Cole*, 326 F.2d at 773; *In re Geisler*, 116 F.3d at 1471.

CONCLUSION OF LAW

Appellant failed to meet his burden of establishing that the Examiner's prima facie case of obviousness is in err.

The rejection of claim 28 under 35 U.S.C. § 103(a) as unpatentable over the combination of Krejci, Boyce I, and Boyce II is affirmed.

Claim 30:

ISSUE

Did Appellant meet his burden of establishing that the Examiner's prima facie case of obviousness is in err?

FINDINGS OF FACT

FF 36. The Examiner finds that Boyce I "teaches dehydration of collagen matrix to form a cross-linked matrix before inoculation with dermal culture (col.12 line[s] 45-61) (Ans. 16).

FF 37. Boyce I teaches a dermal collagen-chondroitin-6-sulfate matrix (Boyce I, col. 12, l. 9). Boyce I teaches that the matrix was cross-linked by thermal dehydration (Boyce I, col. 12, ll. 48-49).

ANALYSIS

Claim 30 is drawn to a method of producing a cultured skin device. The method comprises the following steps:

1. dehydrating an engineered biocompatible reticulated acellular matrix comprised of collagen to form a crosslinked matrix and then inoculating said matrix with cultured dermal cells,

2. incubating the inoculated matrix under conditions to form a cellular lamination layer of dermal cells,
3. inoculating cultured epidermal cells on the dermal cell lamination layer, and
4. incubating under conditions sufficient to form a cultured skin device.

Based on the foregoing evidence (FF 31, 36, and 37) the Examiner concludes that "[o]ne would have been motivated to make dried cross-lin[k]ed matrix because such a preparation can be stored in a dry state for future use" (Ans. 6).

Appellant contends that Krejci "has no disclosure whatsoever to a crosslinked matrix, and his use of cadaver skin teaches away from crosslinking (i.e., there are not crosslinkable components) so that the secondary references fail and the rejection cannot stand" (App. Br. 13). We are not persuaded.

Appellant has failed to provide an evidentiary basis to support his contention that Krejci's matrix does not contain crosslinkable components. It is well settled that argument by counsel cannot take the place of evidence. *In re Cole*, 326 F.2d at 773; *In re Geisler*, 116 F.3d at 1471.

CONCLUSION OF LAW

Appellant failed to meet his burden of establishing that the Examiner's prima facie case of obviousness is in err.

The rejection of claim 30 under 35 U.S.C. § 103(a) as unpatentable over the combination of Krejci, Boyce I, and Boyce II is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

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